**A Text Mining Based Analysis of the**

**Functions of Serotonin Receptor Subtypes**

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**Abstract**

There are at least 14 structurally and functionally distinct serotonin (5-HT) receptor subtypes. These serotonin receptors are each distributed uniquely throughout the central nervous system and can be up, or down, regulated with specific agonists and antagonists. Despite this vast literature, the relationship of individual serotonin receptors to specific behavioral or cognitive functions still remains perplexing. To help better elucidate underlying relationships between receptors and functions, we examined the co-occurrence of specific serotonin receptors and behavioral topics in over 9,600 published articles. Specifically, we utilized simplistic co-occurrence and rule-based text mining procedures to discover associations between receptor subtypes and behavioral topics in causal research on serotonin receptors. Our results from this neuroinformatics approach not only help uncover latent relationships between serotonin receptors and behavioral functions, but also provide a useful guide for directing future research on specific serotonin receptors and behaviors associated with the serotonergic system.

*Keywords*: serotonin, 5-HT, 5-HTR, receptor subtypes, behavior, function, cognition, text mining, co-occurrence

**Introduction**

Serotonin (5-hydroxytryptamine; 5-HT) was first discovered in the central nervous system (CNS) in 1953 (Twarog & Page, 1953). Initially, two 5-HT receptor subtypes were identified and found to have dissociable roles in mediating smooth muscle contractions and depolarizing cholinergic nerves, respectively (Gaddum & Picarelli, 1957). Further, 5-HT receptor subtypes were later identified and reclassified via radioligand binding by Peroutka and Snyder (1979), and the pharmacology of three 5-HT receptor subtype families, 5-HT1-3, was reviewed for the first time several years later (Bradley et al., 1986).

Over time, advances in operational pharmacology and molecular biology have led to the classification of seven different 5-HT receptor families, remarkably consisting of at least 14 major subtypes (potentially even 18 subtypes total, if 5-HT3 is classified into 5-HT3A-E; see Kitson, 2007; Niesler et al., 2007). Classification criteria for 5-HT receptors have been established based upon transduction mechanisms, operational characteristics, second messengers, and amino acid sequencing (Hoyer et al., 1994), and there are multiple reviews of the molecular biology of 5-HT receptors (e.g., Hannon & Hoyer, 2008). Following the classification of 5-HT receptor subtypes, Barnes and Sharp (1999) compiled an in-depth review of the structures, distributions, and functional effects of the 14 primary pharmacologically distinct subtypes. Since then, serotonin receptors have been continuously to be found to be implicated in numerous core behavioral functions, including hunger, sex, modulating mood, learning, memory, emotion and anxiety (see Nichols & Nichols, 2008 for comprehensive review).

However, a clear understanding of which serotonin receptors are casually implicated in specific behavioral functions remains surprisingly elusive despite the wealth of research across different topics and receptors of interest, possibly reflecting the complexity of the serotonergic system in regulating cognition and behavior. Undoubtedly, quantifiably identifying the G-protein effectors, agonists, antagonists, and radioligands for each serotonin receptor is quite challenging (see Hoyer, Hannon, & Martin (2002), Table 2). Similarly, identifying the behavioral topics most closely studied in conjunction with a specific 5-HT receptor also presents a challenge. Even the most widely used neuroscience text books do not adequately discuss the behavioral functional differences between the serotonin receptor subtypes (e.g., Hyman & Cohen, 2013, pp. 1412, Table 63-3). In particular, the vast breadth and depth of serotonin research makes it exceedingly difficult to identify any consensus or trends in associating particular behavioral topics with specific receptors. Manually identifying relationships across all existing relevant literature would require reading, synthesizing, and drawing conclusions from hundreds, if not thousands, of texts. Indeed, contemporary comprehensive review articles on serotonin receptors typically focus on either one specific receptor (e.g., 5-HT1A receptor; Bell & Hobson, 1994), specific topic (e.g., depression; Carr & Lucki, 2011), or particular combination of both (e.g., role of 5-HT1A & 5-HT7 in learning & memory; Stiedl, Pappa, Konradsson-Geuken, & Ögren, 2015). Such reviews provide invaluable insight into their subject of focus – however, they do not holistically assess which behavioral functions have been associated with which serotonin receptors across all available research. Thus, it is extremely difficult to make evidence-based claims about which receptors are most commonly associated with certain behavioral functions.

The abundance of research on serotonin effectively hinders a manual review of identifying the functional roles of serotonin receptors. However, it lends itself particularly well to text mining efforts applied to large, big-data datasets. Text mining has become increasingly popular in biomedical research (see Ambert & Cohen, 2012; French, Lane, Xu, & Pavlidis, 2009). Biomedical text mining allows for researchers to quickly identify needed information, uncover hidden relationships not immediately obvious in the literature, and more generally deal with ‘information overload’ from the exponentially increasing volume of scientific research (Cohen & Hersh, 2004). For example, simplistic keyword indexing has been used for protein annotation and term co-occurrences have been successfully applied create human gene-to-gene expression networks (Jenssen, Lægreid, Komorowski, & Hovig, 2001).

More recently, neuroscientists have begun to utilize text mining and other neuroinformatics approaches (Bockholt et al., 2010). Text mining has been used to extract mentions of neuroanatomical regions from text (French, Lane, Xu, & Pavlidis, 2009), assess connectivity between brain regions (French et al., 2015), and discover associations between text and brain activation in a functional neuroimaging database (Nielsen, Hansen, & Balslev, 2004). However, relative to the tremendous volume of neuroscientific work available, there are surprisingly few text mining studies to date. For example, a search on PubMed for articles containing “neuroscience” and “text mining” or “natural language processing” returns only 134 results (search performed May 7, 2020). Utilization of even very basic text mining procedures may provide valuable insight into latent trends in neuroscience research.

For the serotonergic system, co-occurrence text mining of the serotonin literature can help quantitatively establish proposed relationships between receptors and functions. These relationships can further be analyzed via their trends over time, as well as by performing brief manual literature reviews to complement the co-occurrence results. In the current research, we set out to identify relationships between serotonin receptors and topics of study. Specifically, we aimed to identify which behavioral topics or functions are significantly associated with each of the 14 serotonin receptors across all existing, published, causal studies of serotonin receptors. After collecting all relevant literature and extracting key neuroinformatic data from the literature via pre-determined terms and rule-based regular expressions, we applied probabilistic co-occurrence analysis to assess across-study relationships between serotonin receptors and behavioral topics. For significant co-occurrences with larger effect sizes, we also tracked how said co-occurrences vary in studies across time, with additional brief literature reviews to further inform our results.

The main contribution of the current work is two-fold. First, our meta-analytic findings based on text mining provide a useful guide for directing future research on specific serotonin receptors, as our data can inform researchers about which receptor or behavioral function to examine when designing novel studies within the domain of 5-HT as well as a large catalog of existing research on said topics. Second, our work is an extension of recent efforts to increase the interdisciplinary relationship between neuroscience and natural language processing. Overall, we demonstrate how a big-data driven text mining effort may elucidate important patterns and relationships in neuroscientific domains as complicated as that of serotonin.

**Methods**

**Search strategy.** A systematic literature search was conducted in order to collect all relevant studies pertaining to the causal roles of each serotonin receptor subtype. The search was performed on two databases, PubMed and Web of Science, and was conducted through the date 5 April 2019 with no language restrictions. Our literature search consisted of terms referencing 5-HT receptor subtypes (e.g., “5-HT1A”, “5-HT1B”, “5HT1A”, “5HT1B”), terms referencing specific methods employed in causal studies of serotonin receptors (“agonist”, “antagonist”, “agonism”, “antagonism”, “optogenetics”, “positron emission tomography”, “PET”, “staining”, “stimulation”, “knockdown”, “knockout”, “immimmunohistochemistry”), and the term “brain” in order to hopefully eliminate studies focusing on the gastrointestinal system or peripheral nervous system. Causal methods were selected in order to restrict our search results to independent research on the causal functional roles of receptors, with the goal of excluding reviews, biochemical classification papers, and genetic studies. See Appendix 1 for full search criteria.

**Eligibility criteria**. Our initial PubMed search found 6,764 articles, and our Web of Science search returned 7,436 articles, for a total of 14,200 articles. We then applied following exclusion criteria to our initial articles list. Our criteria included (1) no duplicate articles, (2) no articles in which a specific 5-HT family is not mentioned, and (3) no review articles. 4,569 articles failed at least one part of our exclusion criteria, resulting in a total of 9,631 articles that passed our exclusion criteria. See Figure 1 for the illustrative diagram for the eligibility selection procedure.

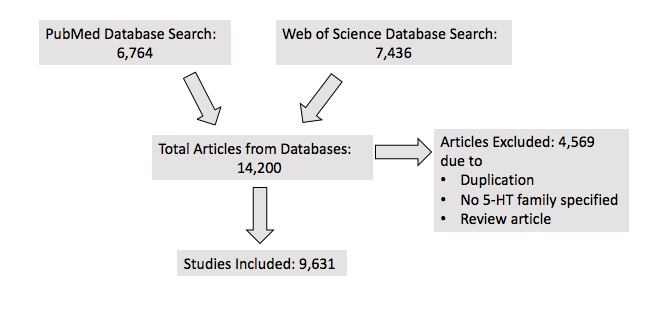


Figure 1. *Diagram of data collection & exclusion criteria application.*

**Text mining**. We transferred the abstracts from all 9,361 articles from EndNote X8 into a single corpus (available at INSERT). Despite research suggesting that full-text articles are better for text mining scientific literature (Westergaard, Stærfeldt, Tønsberg, Jensen, & Brunak, 2018), we specifically used only abstracts for several reasons. First, abstracts consistently only mentioned 5-HT receptors that were actually looked at in the main methods and results of the paper, and did not mention receptors in passing whereas introduction and discussion sections of paper often would mention 5-HT receptors unrelated to the actual contents of the empirical results. Second, although using full-texts is advised when looking at word association assessment, here we were more specifically interested in pulling topics, methods, and other features that are empirically investigated in each paper. For this purpose, the abstracts avoided unnecessary confounding information provided in the introductions and discussions of papers, and included the essentials of our text mining search. ~~Third, many articles did not allow downloading the full text through EndNote X8, and therefore compiling a corpus of only abstracts ensured we would have a complete entry for every article in the database.~~ We also validated our abstracts approach by looking specifically at the abstracts of 5-HT5A manually, as this is the receptor with the fewest number of articles. As expected, we verified that only relevant receptors were mentioned in the abstract, whereas the introduction and discussion often referenced other 5-HT receptors unrelated to the present studies performed.

We used a number of automated information extraction techniques, described below, to retrieve information of interest from each abstract. First, we created a system which took open-sourced and hand-designed lists of topics of study, animal species of study, causal methods of study, agonists and antagonists of 5-HT receptors, and brain regions and automatically generated regular expressions to find matches of those entities in text with either singular or plural inflection. The list of topics of study included 37 possible topics commonly associated with serotonin modulatory function, which we compiled *a priori* (see Appendix 2). This list of topics was compiled from identifying key topics discussed in several comprehensive literature reviews on serotonin (e.g., Barnes & Sharp, 1999), as well as adding additional topics relevant to serotonin which may have been absent from these reviews (e.g., ‘social dominance’; see Weinberg-Wolf & Chang, 2019). Topics were worded such that they would be tagged if they appeared as sub-words in variant expressions of the same topic (e.g., *depress* was used instead of *depression* to catch reference cases such as *depressive*). Species, causal methods, agonists and antagonists, and brain regions were included as additional potentially meaningful information abstracts, and these lists were also created *a priori* based on known associations with serotonin (see full search-lists and results in Supplemental Materials).

Receptors were found via a multi-step rule algorithm that identified substrings consisting of first a family, and then a subtype (e.g., 5-HT1A has family “1” and subtype “A”). The procedure accomplished the extraction by first finding occurrences of ‘5HT’ or ‘serotonin’ (here called the prefix), searching the subsequent text for family names (i.e., 1,2,3,4,5,6, or 7), and then finally the subtype (e.g., 1A, 1B, etc.). Subtypes were optional, but families were not – meaning that the procedure would terminate if no family was found after the prefix. This excluded tagging any mentions of only 5-HT or serotonin *in general*, without reference to a specific receptor.

The field has used highly heterogeneous orthographical conventions (such as beginning a receptor with either 5HT or ‘serotonin’ interchangeably, as well as a number of shorthands for abbreviating lists of receptors (e.g. 5-HT1A/1B or 5-HT1A-B representing instances of both 5-HT1A and 5-HT1B), for describing serotonin receptor types. Additionally, punctuation, capitalization, and use of spaces were highly variable. In order to overcome all of the above peculiarities, the regular expressions ignored non-alphanumeric characters, split lists of elements delimited by ‘/’ or ‘-‘, and used heuristics to determine at each phase which set of subsequent characters constituted a legitimate continuation of the receptor name. Our full data extraction code is provided here (INSERT).

Moreover, we evaluated the accuracy of the receptor-tagging module and have repackaged it as a standalone tagger capable of searching text and extracting the receptors mentioned therein. We evaluated the accuracy by randomly choosing 17 articles from the database and hang-tagging occurrences of receptors as they should be parsed. For instance, by the criteria set out above both “serotonin 1a/b” and “5 HT1a-b” would parse to “5HT1A” AND “5HT1B”, and “5-(HT) 3” would parse to “5HT3”. The parsed receptor instances were left in-place in the abstract and the entire abstract was fed to the receptor tagger. For example, the sentence “serotonin 1a agonist was studied in this paper” would be fed into the tagger with a label indicating the present of “5HT1A” at the start of the document. We thus hand-tagged 113 instances of receptor mentions in the corpus, representing a wide range of the possible spellings and formatting, including uses of “serotonin” in place of “5HT”, lists shorthanded with /, and many capitalizations and spacings. Our automated tagger achieved a precision of 92.3% with a coverage of 95.6%, leaving only less than 5% either mislabeled or absent entirely. This system could prove very useful for other researchers trying to study the occurrence of receptor types in the literature from large, raw text corpora.

Our initial data extraction results showed that over 98% of our selected abstracts referenced at least one 5-HT receptor, and approximately 51% of abstracts included at least one of the 37 pre-determined topics of interest. We thus proceeded with our co-occurrence analysis.

**Probabilistic co-occurrence analyses.** After extracting the proper information from each abstract, we converted our receptor and topics of study data into a binary presence-absence format. We then used the *R* package *cooccur* (see Griffith, Veech, & Marsh, 2016) to run a probabilistic co-occurrence analysis on our receptor and topic data (Veech, 2013). In context, this co-occurrence analysis, adapted from ecological species co-occurrence, measures co-occurrence as the number of abstracts where a certain topic and a certain receptor are both mentioned. This can be compared to the expected co-occurrence, which is simply the product of both topic and receptor occurrence and number of abstracts. P-values can be directly computed from this model as the probability of co-occurrence at a frequency greater than the observed frequency if the receptor and topic were distributed randomly (independently) of one another (see Griffith, Veech, & Marsh, 2016). Furthermore, standard probabilistic co-occurrence effect sizes (i.e., standard effect sizes; SES) may be calculated as the absolute difference between observed and expected frequencies of co-occurrence divided by the total number of abstracts (9,631).

After running probabilistic co-occurrence between all topics and receptors, we identified a multitude of both positive and random relationships. The full results (allowing for co-occurrences within category) may be viewed in the co-occurrence matrix in Figure 2.

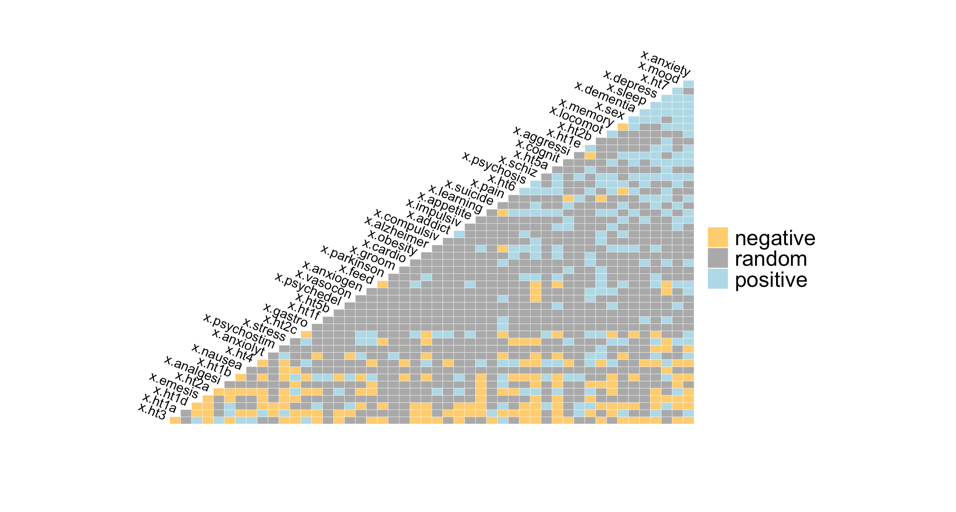


Figure 2. *Co-occurrence matrix between receptors and topics. [I think you need to again describe some basics of this figure in this figure legend so people can just look at get a general idea of what this is]*

**Results**

For each receptor, we identified all significant positive topic co-occurrences, and calculated effect sizes accordingly. Our results provide evidence for at least one significant co-occurrence relationship between receptor subtype and behavioral topic for all but one of our 14 receptors of interest. Altogether, we found 69 significant co-occurrence relationships (summarized in Table 1). In order to examine both the statistical *and* functional validity of these findings, we next examined the literature behind these significant positive co-occurrences.

|  |  |
| --- | --- |
| **Receptor** | **Significant Behavioral Topic Relationships** |
| 5-HT1A | Depression\*\*\*; Anxiolytic\*\*\*; Anxiety\*\*\*; Stress\*\*\*; Sex\*\*\*; Suicide\* |
| 5-HT1B | Aggression\*\*\*, Feeding\*\*\*, Vasoconstriction\*\*\*, Pain\*\*, Impulsivity\* |
| 5-HT1D | Pain\*\*\*, Vasoconstriction\*\*\* |
| 5-HT1E | Pain\*\*\*, Anxiety\*\*, Schizophrenia\*\*, Depression\* |
| 5-HT1F | Pain\*\*\*, Sleep\*\* |
| 5-HT2A | Schizophrenia\*\*\*, Psychedelics\*\*\*, Psychosis\*\*\*, Mood\*\*, Cognition\*, Impulsivity\*, Compulsivity\* |
| 5-HT2B | Cardiovascular\*\*\*, Obesity\*\*\*, Anxiogenic\*\*, Anxiolytic\*\*, Vasoconstriction\* |
| 5-HT2C | Feeding\*\*\*, Appetite\*\*\*, Obesity\*\*\*, Locomotion\*\*, Anxiety\*\*, Anxiogenic\*\*\*, Addiction\*\*, Compulsivity\* |
| 5-HT3 | Emesis\*\*\*, Nausea\*\*\*, Pain\*\*\*, Analgesic\*\*\*, Gastrointestinal\*\*\* |
| 5-HT4 | Memory\*\*\*, Alzheimer’s\*\*\*, Cognition\*\*\*, Gastrointestinal\*\*\*, Learning\*\*\*, Pain\* |
| 5-HT5A | Learning\* |
| 5-HT5B | n/a |
| 5-HT6 | Cognition\*\*\*, Memory\*\*\*, Learning\*\*\*, Alzheimer’s\*\*\*, Schizophrenia\*\*\*, Dementia\*\*\*, Obesity\*\*\*, Psychosis\*\* |
| 5-HT7 | Memory\*\*\*, Sleep\*\*\*, Cognition\*\*\*, Learning\*\*\*, Mood\*\*\*, Pain\*\*\*, Schizophrenia\*\*\*, Dementia\*\*, Cardiovascular\*, Depression\* |

\*p < .05, \*\*p < .01, \*\*\*p < .001

Table 1. *Summary of significant co-occurrence relationships between receptors and behavioral topics.*

**5-HT1A**

The 5-HT1A receptor was most represented in our corpus of abstracts being referenced in 5,283 studies, and 3,492 studies with a topic of interest identified. Our probabilistic co-occurrence analysis identified six topics that significantly co-occurred with the 5-HT1A receptor. These results are displayed in Table 2.

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Depression** | 821 | < .001 | .012 |
| **Anxiolytic** | 365 | < .001 | .010 |
| **Anxiety** | 486 | < .001 | .007 |
| **Stress** | 401 | < .001 | .005 |
| **Sex** | 178 | < .001 | .004 |
| **Suicide** | 33 | .023 | .001 |

Table 2. *Probabilistic co-occurrence results between 5-HT1A and behavioral topics.*

**5-HT1A and Depression & Suicide.** The serotonergic system has long been implicated in depression, and serotonin receptors have been targeted especially due to the widespread clinical use of serotonin reuptake inhibitors as antidepressants (for reviews, see Carr & Lucki, 2011; Kaufman, DeLorenzo, Choudhury, & Parsey, 2016). Dysfunction of the 5-HT1A receptor has been suggest to play a key role in major depressive disorder (Savitz, Lucki, & Drevets, 2009), and numerous studied have indicated that 5-HT1A receptor agonists such as 8-OH-DPAT and ipsapirone produce antidepressant-like effects (Table 2, Carr & Lucki, 2011; Lucki, 1991; though note that 8-OH-DPAT is also a 5-HT7 agonist, for e.g., see Hedlund et al., 2004). Such antidepressant effects are hypothesized to be due to 5-HT1A receptor mediation of hippocampal neurogenesis, which is produced by multiple types of antidepressants (Malberg, Eisch, Nestler, & Duman, 2000). Furthermore, both presynaptic and postsynaptic 5-HT receptors have been implicated in depression. As summarized by Carr and Lucki (2011), presynaptic 5-HT1A receptors are associated with risk for depressive behavior, and postsynaptic 5-HT1A receptors are instrumental towards producing agonistic antidepressant-like effects, and may also contribute to the efficacy of SSRIs. However, 5-HT1A receptor agonists, including both selective full (e.g., azapirones at autoreceptors) and partial agonists (e.g., gepirone), have suffered from a poor clinical success rate thus far, though this is perhaps due to administration in a suboptimal manner. (Blier & Ward, 2003).

Additionally, the biological underpinnings of suicide have been often studied via 5-HT1A receptors. Suicide victims exhibit alterations in agonist-stimulated 5-HT1A receptor activation (Hsiung et al. 2003) and post-mortem studies have discovered lower densities of 5-HT1A receptors in the hippocampus, amygdala, and ventral prefrontal cortex (Cheetham, Crompton, Katona, & Horton, 1990; Bowen, Najlerahim, Procter, Francis, & Murphy, 1989). However, recent studies have failed to identify differences in 5-HT1A receptor binding between control and depressed groups, or between depressed suicide attempters and non-attempters (Mann et al., 2019), and other results suggest that prior findings are perhaps due to 5-HT1A receptor function being affected by co-morbid alcoholism (Savitz, Lucki, & Drevets, 2009).

**5-HT1A and Anxiety, Anxiolytic Function, & Stress.** Since the late 1990s, 5-HT1A knockout mice have been used as animal models of anxiety disorders (Ramboz et al., 1998; Toth, 2003). A causal relationship between 5-HT1A and anxiety is demonstrated by the finding that 5-HT1A selective agonists such as flesinoxan ameliorate stress-related behaviors in rats when injected into the amygdala and hippocampus (Li et al., 2006). Recent work has even provided neurodevelopmental evidence of a causal implication, as disrupted 5-HT1A function in adolescence promotes sustained increases of anxiety in mice (Garcia-Garcia, Meng, Richardson-Jones, Dranovsky, & Leonardo, 2016). With regards to stress, 5-HT1A autoreceptor levels are related to resilience under stress (Richard-Jones et al., 2010). 5- HT1A have also been found to modulate anxiety-like behavior in mice exhibiting post-traumatic stress disorder (Xiang *et al.*, 2019). More recently, optogenetics has further illuminated the role of 5-HT1A, demonstrating that activation of the receptors localized to the bed nucleus of the stria terminalis, a major subdivision of the amygdala, is necessary for the anxiolytic effects observed (Garcia-Garcia *et al.*, 2018).

**5-HT1A and Sex.** Our results also indicated a significant relationship between 5-HT1A and sex, albeit with a small effect size (Table 2). The sexual dysfunction brought about by SSRIs is a well-studied phenomena (Montejo-Gonzalez et al., 1997; for recent literature review, see Bala, Nguyen, & Hellstrom, 2018). 5-HT1A activation has been differentially linked to female and male sexual behavior in rats, inhibiting sexual behavior in females while enhancing sexual behavior in males and females treated with testosterone (Mendelson & Gorzalka, 1986). However, further studies reveal an even more complex relationship, with some 5-HTA agonists inhibiting and other agonists promoting sexual behavior in rats (Rehman et al., 1999). Recently, it has been hypothesized that drugs with partial 5-HT1A agonism may mitigate sexual dysfunction induced by SSRIs (Oosteing, Chan, Olivier, & Banerjee, 2016).

**5-HT1B**

5-HT1B was referenced in 1,462 studies, 678 of which also included a topic of interest. Five significant topic relationships were found with the 5-HT1B receptor (Table 3).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Aggression** | 71 | < .001 | .004 |
| **Feeding** | 87 | < .001 | .003 |
| **Vasoconstriction** | 30 | < .001 | .002 |
| **Pain** | 63 | .001 | .002 |
| **Impulsivity** | 22 | .023 | .001 |

Table 3. *Probabilistic co-occurrence results between 5-HT1B and behavioral topics.*

**5-HT1B and Aggression & Impulsivity.** 5-HT1B knockout mice demonstrate increased aggressive behavior, such as attacking intruding mice more quickly and intensely relative to wild-type mice (Saudou et al., 1994; Ramboz et al., 1995). Furthermore, 5-HT1B receptor agonists have been shown to have anti-aggressive effects (de Boer & Koolhaas, 2005). Given such findings, it has been hypothesized that postsynaptic 5-HT1B modulate aggression (see Olivier & Oorschot, 2005, for review).

It has also been proposed that the hyper-aggressive phenotype observed in 5-HT1B knockout mice may be a result of changes in impulsivity and impulsive control, rather than aggression per se (e.g., Brunner & Hen, 1997), as 5-HT1B knockout mice also exhibit impaired impulse control in addition to increased aggressive tendencies (Bouwknecht et al., 2001). However, more recent evidence suggests that aggressive and impulsive behaviors are modulated via distinct mechanisms, both involving the 5-HT1B receptor (Nautiyal et al., 2015).

**5-HT1B and Feeding.** In addition to higher cognitive functions, serotonin is also strongly implicated in feeding and satiety behaviors (Simansky, 1995). In particular, 5-HT1B agonists, along with 5-HT1A agonists, have been found to reduce food intake and induce anorexia in rats (Bendotti & Samanin, 1987; Kennett, Dourish, & Curzon, 1987). Moreover, selective 5-HT1B agonist CP-94,253 have been found to promote satiety and decrease food consumption (Lee & Simansky, 1997; Halford & Blundell, 1996).

**5-HT1B and Vasoconstriction & Pain.** The significant co-occurrence relationship between 5-HT1B and vasoconstriction is most likely due to the fact that 5-HT1B receptors mediate serotonin-induced constriction of human cerebral arteries (Nilsson, Longmore, Shaw, Olesen, & Edvinsson, 1999). Vasoconstriction of the middle meningeal artery has been shown to be mediated nearly selectively via the 5-HT1B (Razzaque et al., 1999). These findings have been related to migraines, perhaps explaining the association in our data between 5-HT1B and pain (e.g., Cumberbatch, Williamson, Mason, Hill, & Hargreaves, 1999).

**5-HT1D**

Our results indicate that a total of 592 studies referenced the 5-HT1D receptor, and 315 of these mentioned a topic of interest. Only two significant topic relationships were discovered via probabilistic co-occurrence analysis (Table 4).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Pain** | 51 | < .001 | .003 |
| **Vasoconstriction** | 28 | < .001 | .003 |

Table 4. *Probabilistic co-occurrence results between 5-HT1D and behavioral topics.*

**5-HT1D and Vasoconstriction & Pain.** Similar to 5-HT1B, 5-HT1D receptors have been shown to induce vasoconstriction of cranial vessels and have thus been associated with migraines (Negro, Koverech, & Martelletti, 2018). A family of selective agonists, known as triptans, have been found to act on these receptors, thereby inhibiting the release of inflammatory neuropeptides and subduing the pain associated with migraines (Blumenfeld, Gennings, & Cady, 2012). While 5-HT1D receptors are mostly found in cranial vessels, they are also found in peripheral vessels such as the coronary and limb arteries. For this reason, the same agonists for 5-HT1D have been suspected to cause adverse chest pain through mild vasoconstriction (Ishida *et al.*, 1998).

**5-HT1E**

5-HT1E was one of the least mentioned receptors in our corpus, and was mentioned in only 39 studies, with 33 including a topic of interest. Our results suggest four significant topic co-occurrence relationships (Table 5).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Pain** | 7 | < .001 | .001 |
| **Anxiety** | 9 | .003 | .001 |
| **Schizophrenia** | 7 | .004 | .001 |
| **Depression** | 10 | .028 | < .001 |

Table 5. *Probabilistic co-occurrence results between 5-HT1E and behavioral topics.*

**5-HT1E and Anxiety & Depression.** Studies using immunohistochemistry and western blotting have been able to accurately localize the 5-HT1E receptor to the dentate gyrus of the hippocampus. Stimulation of the receptor using a selective agonist was shown to inhibit hippocampal activity, suggesting that the receptor may be a negative modulator of neural plasticity (Klein and Teitler, 2012). This role may explain the association between 5-HT1E and depression as changes to neural plasticity (including decreased synaptic plasticity, reduced neurogenesis, impaired LTP, and enhanced LTD) has been implicated in the onset and development of depression (Liu *et al.*, 2017).

**5-HT1E and Schizophrenia.** The role of 5-HT1E in reducing hippocampal activity may also explain the relationship between the receptor and schizophrenia. Hippocampal hyperactivity has been linked to temporal lobe epilepsy, which is commonly studied as a comorbidity for schizophrenia (Cascella, Schretlen, & Sawa, 2009).

**5-HT1E and Pain.** In addition to agonists acting on the hippocampal 5-HT1E receptors, other agonists with high affinity for 5-HT1E have been discovered to cause potent contraction of the aorta (McKune & Watts, 2001). This may explain the association between the receptor and pain found in our data, as vasoconstriction of major arteries may lead to angina and other forms of chest pain (Ishida *et al.*, 1998).

**5-HT1F**

74 studies referenced the 5-HT1F receptor, with 25 of these studies mentioning a topic of interest. Our analyses revealed only two significant topic relationships (Table 6).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Pain** | 18 | < .001 | .002 |
| **Sleep** | 7 | .002 | .001 |

Table 6. *Probabilistic co-occurrence results between 5-HT1F and behavioral topics.*

**5-HT1F and Pain.** Since the late 1990s, 5-HT1F agonists have been shown to inhibit neurogenic dural inflammation, suggesting that this receptor may be a target for migraine therapeutics and establishing a potential explanation for the link between 5-HT1F and pain (Johnson *et al.*, 1997; Phebus *et al.*, 1997). More recently, clinical trials have confirmed the ability of 5-HT1F agonists to successfully abort migraine attacks without some of the vasoconstrictory side effects of other therapeutics targeting the 5-HT1B/D receptors (Neeb, Meents, & Reuter, 2010; Akerman, Romero-Reyes, & Holland, 2012).

**5-HT1F and Sleep.** While studies directly linking 5-HT1F and sleep are limited, their association may also be explained by the role of 5-HT1F in migraine relief. As one comprehensive review shows, one of the most common side effects found in clinical trials for targeted 5-HT1F therapies include somnolence, fatigue, and lethargy (Vila-Pueyo, 2018).

**5-HT2A**

The 5-HT2A receptor was the second most referenced after the 1A receptor, mentioned in 2,595 papers. 1,778 of these papers also referenced a topic of interest. Our analyses revealed seven significant topic relationships (Table 7).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Schizophrenia** | 281 | < .001 | .015 |
| **Psychedelics** | 38 | < .001 | .003 |
| **Psychosis** | 55 | < .001 | .003 |
| **Mood** | 109 | .008 | .002 |
| **Cognition** | 181 | .025 | .002 |
| **Impulsivity** | 36 | .010 | .001 |
| **Compulsivity** | 17 | .018 | .001 |

Table 7. *Probabilistic co-occurrence results between 5-HT2A and behavioral topics.*

**5-HT2A and Schizophrenia, Psychedelics, & Related Topics.** The 5-HT2A receptor has been widely studied in association with various neuropsychiatric and neurodegenerative disorders, largely due to its role as a therapeutic target for several hallucinogens, antipsychotics, and antidepressants. Many early studies demonstrated the affinity of both classes of hallucinogens (indoleamines and the phenethylamines), to 5-HT2A as well as the ability of these agents to elicit hallucinogenic effects by acting as an agonist to activate the receptor (Mckenna *et al.*, 1990; Aghajanian & Marek, 1999). Closely related to hallucination is psychosis, a mental condition characterized by a loss of touch with reality that may or may not involve hallucinations. Early studies have additionally shown that agonists for the receptor can also increase psychosis while antagonists for the receptor can decrease psychosis and psychosis-like behaviors (Schmidt *et al.*, 1995; Meltzer, 1999; Umbricht *et al.*, 2002). These therapeutic effects have been well documented in a number of disease models including schizophrenia, Parkinson’s, and Alzheimer’s, underscoring the complex and diverse pathophysiologies of psychosis through serotonergic receptors (Nyberg *et al.*, 1999; Price, Bonhaus, & McFarland, 2012).

More recent studies have also proposed additional functions of the 5-HT2A receptor, as analyses in postmortem patients established a significant correlation between global reduction of 5-HT2A binding and cognitive impairments, depression, and anxiety (Hasselbalch *et al.*, 2008). However, both agonists and antagonists for the receptor have been shown to enhance and block various different forms of memory consolidation and learning (i.e. contextual fear memory, object memory, declarative memory, spatial learning), suggesting that 5-HT2A may have a complex influence on cognition (Harvey, 2003; Boulougouris, Glennon, & Robbins, 2008; Bekinschtein *et al.*, 2013). These results are likely due to the fact that serotonergic fibers innervate various important nodes such as the prefrontal cortex, which is implicated in decision making, cognitive control, and emotional regulation among other functions, as well as many critical nodes in the temporal lobe memory system, including the amygdala and hippocampus (Zhang & Stackman, 2015).

Given all these clinical findings, antagonists for 5-HT2A have been most well studied as a treatment for schizophrenia due to its ability to simultaneously target multiple symptoms of the disorder including psychosis, affective distortions, and cognitive impairment (Poyurovsky *et al*., 2003; Meltzer, Massey, & Horiguchi, 2012; ).

**5-HT2A and Impulsivity & Compulsivity.** Well characterized antagonists to 5-HT2A have allowed for greater understanding of the association between the receptor subtype and two closely related behaviors, impulsivity and compulsivity. These antagonists have been shown to decrease premature responses and cue reactivity, using common measures of impulsivity such as the choice serial reaction time test (Winstanley *et al.*, 2004; Scholler *et al.*, 2018). Furthermore, antagonists to 2A were found to inhibit agents that reduced compulsive behaviors, establishing the therapeutic potential of 5-HT2A to modulate compulsivity (Navarro *et al.*, 2015). The interactions of 5-HT2A with reward pathways of the brain may be at the foundation of these effects, as studies have demonstrated that antagonists to 2A can significantly reduce amphetamine-induced dopamine release and that patients with obsessive compulsive disorder show higher concentration of 5-HT2A receptors and increased binding in the caudate nucleus (Porras *et al.*, 2002; Adams *et al*., 2005).

**5-HT2B**

The 5-HT2B receptor was mentioned in 339 papers, with 74 including a topic of interest, and we discovered five significant topic relationships (Table 8).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Cardiovascular** | 13 | < .001 | .001 |
| **Obesity** | 10 | < .001 | .001 |
| **Anxiogenic** | 14 | .001 | .001 |
| **Anxiolytic** | 29 | .005 | .001 |
| **Vasoconstriction** | 6 | .015 | < .001 |

Table 8. *Probabilistic co-occurrence results between 5-HT2B and behavioral topics.*

**5-HT2B and Cardiovascular & Vasoconstriction.** Early studies in the 1990s established the expression of 5-HT2B in the myocardium, or muscular tissue of the heart (Choi & Maroteaux, 1996). Since then, further investigations have elucidated the role of the receptor in cardiovascular disease and vasoconstriction. For example, mutations in the 5-HT2B receptor have been shown to cause cardiomyopathy and disruption of intercalated discs, suggesting that the receptor may play a role in regulating cardiac structure and function (Nebigil *et al.*, 2001). This may in part be explained by the influence of 5-HT2B onthe NAD(P)H pathway, as receptor blockade has been shown to prevent increased NAD(P)H oxidase activity and hypertrophy (Monassier *et al.*, 2008). Moreover, antagonists against 5-HT2B have been shown to reduce vasoconstriction, suggesting that the receptor has a role in mediating this behavior (Fernandez *et al.*, 2000).

**5-HT2B and Obesity.** In addition to the CNS and myocardium, 5-HT2B receptors have also been located extensively throughout the gastrointestinal tract (Vickers & Dourish, 2004). Agonists for the receptor have been shown to increase eating behavior in mice. Furthermore, while there is no evidence that antagonists to 2B affect eating behavior alone, pretreatment of the receptor with antagonist blocks the ability of agonists to initiate food intake (Kennett, Ainsworth, & Blackburn, 1997). Later studies have additionally linked 5-HT2B to diabetes, demonstrating that signaling through 2B promotes gluconeogenesis and increased expression of the receptor during gestation leads to β-cell proliferation (Oh, Park, & Kim, 2016).

**5-HT2B and Anxiolysis & Anxiogenisis.** Our results also indicated a significant relationship between 5-HT2B and anxiety. This has been well documented in many mouse and rat models using common measures of anxiety: agonists for the receptor have been shown to increase total interaction in the social interaction test and decreased suppressed response in the four plates conflict test, consistent with anxiolytic properties, while antagonists have been shown to increase suppressed responding in the Geller-Seifter conflict test, marmoset conflict test, consistent with anxiogenic properties (Kennett *et al.*, 1995; Dhonnchadha *et al.*, 2003; Quesseveur *et al.*, 2012). However, the anxiety measures from typical studies do not improve significantly upon conventional anxiolytic drugs such as benzodiazepines and chlordiazepoxides, perhaps explaining the lack of research on 5-HT2B agonists as a treatment option for humans. Interestingly, Duxon *et al*. (1997) showed that injection of the agonist in the medial amygdaloid nuclei led to decreased anxiolytic effects with the social test but not with the conflict test. This result suggests that neurotransmission in this region may selectively affect different kinds of anxiety.

**5-HT2C**

The 5-HT2C receptor was referenced in 1,666 papers, with 947 papers including a topic of interest, and significantly co-occurred with eight different behavioral topics (Table 9).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Feeding** | 105 | < .001 | .004 |
| **Appetite** | 43 | < .001 | .003 |
| **Obesity** | 47 | < .001 | .003 |
| **Locomotion** | 125 | .001 | .003 |
| **Anxiety** | 160 | .004 | .003 |
| **Anxiogenic** | 47 | < .001 | .002 |
| **Addiction** | 33 | .003 | .001 |
| **Compulsivity** | 13 | .011 | .001 |

Table 9. *Probabilistic co-occurrence results between 5-HT2C and behavioral topics.*

**5-HT2C and Feeding, Appetite, & Obesity.** Many studies have demonstrated the therapeutic potential of targeting 5-HT2C for the treatment of obesity and related issues. In the late 1990s, studies began to demonstrate the ability of a 5-HT2C agonist, m-chlorophenylpiperazine (mCPP), to significantly reduce body weight as well as subjective hunger ratings in human subjects. These results additionally indicated elevated plasma prolactin levels, a hormone secreted by the pituitary gland in response to eating among other behaviors, thereby providing a potential molecular basis for the observed reduction in appetite (Sargent *et al.*, 1997; Halford *et al.*, Smith, Thomsen, & Grottick, 2005). However, despite promising initial results, mCPP has been linked to side effects due to the additional selectivity for 5-HT1B. A new generation of selective agonists including Lorcaserin have since been developed and marketed, with more limited side effects (Halford *et al.*, 2010). New research has also altered our understanding of the receptor. While some antagonists with high affinity produce marked effects on feeding behavior, other antagonists do not show the same results unless treatment is combined with antagonists for the H1 histamine receptor (Abela *et al.*, 2020), indicating the importance of pharmacological interactions. Moreover, another study demonstrated the ability of 5-HT2C antagonists to reduce food intake may be a consequence of its ability to enhance reversal learning, improving decision-making strategies overall (Diaz, Wilson, & Howell, 2018). Both of these recent studies thus suggest that 5-HT2C may not have as direct of a role as previously understood.

**5-HT2C and Compulsivity, Addiction, and Locomotion.** Closely related to feeding are reward pathways of the brain. Thus, it is unsurprising that our results also indicated a relationship between 5-HT2C and compulsivity, addiction, and locomotion. The mCPP agonist which decreased feeding in aforementioned studies was also shown to induce hypolocomotion. These results additionally indicated a downregulation of 5-HT2C receptors in limbic areas including the striatum and nucleus accumbens (Fone *et al.*, 2009). Given the interaction between 5-HT2C and dopamine systems, it has thus been hypothesized that the serotonergic receptor may have effects on drug dependency and other compulsive behaviors. For example, Agonists for 5-HT2C have demonstrated ability to reduce nicotine-induced activity (Gottick, Corrigall, & Higgins, 2001). Furthermore, 5-HT2C knockout mice have displayed behaviors indicating compulsive symptomology. For example, these mice have displayed increased chewing of non-nutritive clay, neat chewing patterns on plastic mesh screens, and reduced habituation of head dipping as well as elevated levels of lever pressing for cocaine injection, indicating higher levels of drug reinforcement and addiction (Rocha *et al.*, 2002; Chou-Green *et al.*, 2003).

**5-HT2C and Anxiety.** Early studies using mCPP, a common 5-HT2C agonist, have also led to improved understanding of the association between the receptor and anxiety. Researchers have discovered that mCPP induces a non-linear, dose-dependent increase in anxiety symptoms, such as decreased exploration and decreased social interaction in animal models and increased panic attacks and increased cortisol levels in human subjects. (Kahn *et al*., 1990; Benjamin, Lal, & Meyerson, 1990). Later studies using more advanced genetic manipulations confirmed these results. Using virally injected 5-HT2C sequences in the amygdala, researchers demonstrated that increased expression of 5-HT2C led to anxiogenic effects (Li *et al.*, 2012). Accordingly, mice with 5-HT2C knockout exhibited the opposite results, with anxiolytic effects measured in the elevated maze, mirrored, chamber, and novel object tests. These results further indicated that this effect coincided with a blunting of ACTH in response to anxiety inducing stimuli (Heisler *et al.*, 2007)

**5-HT3**

A total of 2,029 papers mentioned the 5-HT3 receptor, and 934 mentioned both the receptor and a topic of interest. This receptor significantly co-occurred with five different behavioral topics (Table 10).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Emesis** | 90 | < .001 | .004 |
| **Nausea** | 61 | < .001 | .003 |
| **Pain** | 93 | < .001 | .003 |
| **Analgesic** | 48 | < .001 | .003 |
| **Gastrointestinal** | 44 | < .001 | .003 |

Table 10. *Probabilistic co-occurrence results between 5-HT3 and behavioral topics.*

**5-HT3 and Nausea & Related Topics.** The use of agents targeting the 5-HT3 receptor have been well documented for analgesic and antiemetic effects. As early as 1989, researchers were able to demonstrate the ability of 5-HT3 antagonists to act as a peripheral analgesic to reduce inflammatory pain (Giordano & Rogers, 1989) and relieve pain and discomfort in patients experiencing irritable bowel syndrome (Camilleri *et al.*, 1999). More commonly, antagonists to 5-HT3 including Ondansetronhave been studied and confirmed as strong antiemetics, reducing postoperative nausea and vomiting in double-blind studies (Leeser & Lip, 1991; Scuderi *et al.*, 1992). This may be attributed to the role that these antagonists play in binding vagal nerves in the gut and regions of the central nervous system involved in emesis such as the nucleus tractus solitarii and chemoreceptor trigger zone (Gan, 2005). Interestingly, one study using Ondansetron in combination with postoperative analgesics found that the antagonist attenuated analgesic effects, suggesting that 5-HT3 receptors interact with the same antinociceptive pathways (Arcioni *et al*., 2002).

**5-HT4**

The 5-HT4 receptor was discussed in 697 papers, 422 with topic, and significantly co-occurred with six topics (Table 11).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Memory** | 73 | < .001 | .005 |
| **Alzheimer’s** | 41 | < .001 | .003 |
| **Cognition** | 56 | < .001 | .003 |
| **Gastrointestinal** | 28 | < .001 | .003 |
| **Learning** | 35 | < .001 | .002 |
| **Pain** | 24 | .018 | .001 |

Table 11. *Probabilistic co-occurrence results between 5-HT4 and behavioral topics.*

**5-HT4 and Memory & Related Topics.** The 5-HT4 receptor subtype has been extensively studied in relation to memory, learning, and cognition. Selective agonists for 5-HT4 have consistently led to enhanced memory and improved learning as measured by the Morris water maze, the object recognition, spatial alternation, autoshaping, passive avoidance, matching-to-sample, five-choice serial reaction time, and olfactory associated learning tests. In these tests, selective antagonists for 5-HT4 have consistently led to decreased memory and impaired cognition (Meneses & Hong, 1997; Marchetti *et al.*, 2007; Mohler *et al.*, 2007; for review, see Hagena & Manahan-Vaughan, 2017). Many studies have attributed these effects to the ability of 5-HT4 to modulate acetylcholine release and synaptic plasticity in the hippocampal and prefrontal cortical regions. In mouse models, selective agonists have been shown to increase acetylcholine release, augment long-term potentiation, attenuate depotentiation, and alternate patterns of long-term depression (Matsumoto *et al.*, 2001; for review, see King, Marsden, & Fone, 2008). Furthermore, agonists have demonstrated the ability to improve neuronal survival and inhibit the generation of ß-amyloid proteins, two qualities commonly associated with Alzheimer’s Disease (Cho & Hu, 2007). Given all of these results, many of these papers have discussed 5-HT4 as a potential target for Alzheimer’s Disease therapies. However, research on this matter does not seem to have progressed past pre-clinical testing as of 2020.

**5-HT4 and Gastrointestinal & Pain.** The effects of agonists for 5-HT4 in the gastrointestinal tract have been studied in both healthy and unhealthy subjects. The use of agonists in dog models have resulted in enhanced motility in various regions of the gastrointestinal tract, likely due to an associated release of acetylcholine in local muscles (Mine *et al.*, 1997; Taniyama *et al.*, 2000). Successful treatments including Tegaserod have since been developed and tested using double-blind studies in healthy subjects as well as patients with Irritable bowel syndrome or IBS. In healthy subjects, Tegaserod accelerated gastric emptying and transit in both the small intestine and colon. In IBS patients, this treatment was able to provide relief of symptoms including abdominal pain and discomfort, bloating, and constipation (Degen *et al.*, 2001; Muller-Lissner *et al.*, 2001).

**5-HT5A**

The 5-HT5A receptor was a less commonly studied receptor, and was only discussed in 51 papers with only 5 of these papers also referenced a specific topic of interest. Furthermore, it only significantly co-occurred with one topic (Table 12). Additionally, the 5-HT5B receptor, which is only found in rodents and not humans, was mentioned in only 10 articles and did not have any significant topic co-occurrences. Therefore, only 5-HT5A results are presented in the current research.

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Learning** | 5 | .023 | < .001 |

Table 12. *Probabilistic co-occurrence results between 5-HT5A and behavioral topics.*

**5-HT5A and Learning.** 5-HT5A is arguably one of the least studied and understood serotonin receptors due to the fact that it lacks specific ligands. In fact, only partial agonists for the receptor have been found as of 2020. One earlier study by Gonzalez, Chavez-Pascacio, & Meneses demonstrated that antagonists for 5-HT5A led to poor performance in an autoshaping task, which involves learning the conditioned response of a lever-press (2013). This result implied that activation of 5-HT5A could improve learning. In contrast, however, later studies showed that antagonists could ameliorate working memory deficits and improve reference memory in animal models associated with dementia (Yamazaki *et al.,* 2015). The same authors later discovered a possible mechanism for these effects, through the increased release of dopamine and gamma aminobutyric acid (GABA) in the prefrontal cortex of their cognitive dysfunction model (Yamazaki *et al.,* 2018). Nava, Garcia, & Meneses addressed these contradictions by discussing advancements in instruments and tasks used to measure memory, comparing the lever-press from Gonzalez *et al*. to new tasks using nose-pokes. In their studies, combination of the same antagonist with the nose-poke task allowed for increased conditioned responses and reduced variability between subjects, suggesting overall that antagonism of 5-HT5A has a positive effect on learning (2019).

**5-HT6**

The 5-HT6 receptor was referenced in 443 papers, with 354 of these papers including a topic of interest, and significantly co-occurred with eight topics (Table 13).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Cognition** | 94 | < .001 | .008 |
| **Memory** | 66 | < .001 | .005 |
| **Learning** | 48 | < .001 | .004 |
| **Alzheimer’s** | 48 | < .001 | .004 |
| **Schizophrenia** | 53 | < .001 | .004 |
| **Dementia** | 9 | < .001 | .001 |
| **Obesity** | 16 | < .001 | .001 |
| **Psychosis** | 9 | .002 | .001 |

Table 13. *Probabilistic co-occurrence results between 5-HT6 and behavioral topics.*

**5-HT6 and Memory & Related Topics.** The association between 5-HT6 and topics related to memory and cognition have been well studied. Many reviews have been published, summarizing the positive effects of silencing 5-HT6 expression and using antagonistic agents to 5-HT6, including increased memory retention and consolation and overall improved performance on diverse memory and learning paradigms (cites of some of these “many reviews”). These results were linked to elevated extracellular levels of a number of neurotransmitters important in cognition such as acetylcholine, dopamine, glutamate, and GABA in prefrontal cortical regions, the hippocampus, and the striatum (Russell & Dias, 2002; Mitchell & Neumaier, 2005; King, Marsden, & Fone, 2008; Upton *et al.*, 2008). Conversely, agonists have elicited diverse effects in a number of different types of memory tasks. For example, agonists for 5-HT6 led to impairments in autoshaping operant learning and social recognition tasks, but improved memory in attentional set-shifting and fear motivated learning tasks, suggesting that the mechanism may be more complicated than expected (Woods *et al.*, 2012). Antagonists to 5-HT6 have been extensively studied in phase I and II clinical trials for Alzheimer’s Disease treatment with early results attaining appropriate levels of safety, tolerability, and efficacy (Maher-Edwards *et al.* 2010; Codony, Vela, & Ramirez, 2011). However, many more recent Phase 3 trials have failed to show statistical significance and have thus been discontinued (Andrews, Tousi, & Sabbagh, 2018).

**5-HT6 and Schizophrenia & Related Topics.** Cognitive deficits have increasingly been recognized as a core feature of schizophrenia. Thus, similar antagonists for 5-HT6 have also been explored as potential treatments for schizophrenia with limited success. Research has shown that 5-HT6 antagonists can reduce negative symptoms such as impaired cognition and learning in schizophrenia animal models (Pouzet, Didriksen, & Arnt, 2002; Andreas *et al.*, 2011). This may be related to the receptor’s ability to activate mTOR signaling in the prefrontal cortex (Meffre *et al.*, 2012). However, despite the high affinity of antipsychotic agents with 5-HT6, there is no significant evidence supporting antagonists’ ability to reduce positive symptoms such as psychosis in schizophrenia models (Arnt & Olsen, 2011).

**5-HT6 and Obesity.** The significant co-occurrence between 5-HT6 and obesity is likely due to the fact that it is widely studied as a potential weight-loss therapy. A number of studies have shown that antagonists for 5-HT6 lead to decreased food intake, sustained weight loss, and improvement in regards to a number cardio-metabolic risk factors (Holenz *et al.*, 2006; Heal *et al.*, 2008). Furthermore, knockout studies show that mice with nonfunctional 5-HT6 receptors also demonstrate reduced food consumption and reduced weight gain (Frassetto *et al.*, 2008). However, there has since been little data to support its therapeutic role in human trials.

**5-HT7**

The 5-HT7 receptor was discussed in 742 papers, 534 of which included a topic of interest. It also significantly co-occurred with ten topics, the most of any receptor. (Table 14).

|  |  |  |  |
| --- | --- | --- | --- |
| **Topic** | **Co-occurrences** | **P-Value** | **Standard Effect Size** |
| **Memory** | 75 | < .001 | .005 |
| **Sleep** | 54 | < .001 | .004 |
| **Cognition** | 68 | < .001 | .003 |
| **Learning** | 46 | < .001 | .003 |
| **Mood** | 41 | < .001 | .002 |
| **Pain** | 37 | < .001 | .002 |
| **Schizophrenia** | 53 | < .001 | .002 |
| **Dementia** | 9 | .006 | .001 |
| **Cardiovascular** | 13 | .022 | .001 |
| **Depression** | 91 | .047 | .001 |

Table 14. *Probabilistic co-occurrence results between 5-HT7 and behavioral topics.*

**5-HT7 and Memory & Related Topics.** Our results indicated a strong association between 5-HT7 and various topics related to memory and cognition. This has been a well-studied field, with many review articles summarizing the diverse experimentation and inconsistent results (cite some of these here). Many antagonistic agents and 5-HT7 knockout mouse models have produced impairments to memory and learning in spatial and contextual learning tasks (novel object recognition, novel location recognition, Barnes maze, fear conditioning) and non-spatial learning tasks (passive avoidance, instrumental condition, autoshaping). However, many other knockout models and agents have led to insignificant results as well, suggesting that targeting the receptor alone cannot address all cognitive impairments (Meneses, 2004; Stiedl *et al.,* 2015; for review, see Roberts & Hedlund, 2012). On the other hand, experimentation on 5-HT7 agonists have had more consistent results. Agonists have been shown to induce pro-cognitive and pro-amnesic effects, improving performance in many of these same tasks related to learning and memory and reducing symptoms of amnesia. These positive results have been associated with increased cAMP production, an important mediator of signaling pathways involved in memory formation and learning. (Zarefopoulos & Papatheodoropoulos, 2016; Cifariello, Pompili, & Gasbarri, 2008)

**5-HT7 and Schizophrenia.** Our results indicated a strong co-occurrence between 5-HT7 and schizophrenia because it is commonly used as an effective treatment for the disorder. Antagonists for 5-HT7 have shown promising therapeutic effects in both positive and negative symptoms of schizophrenia including attenuation of hyperlocomotion, improved prepulse inhibition response, and enhanced social interaction (Waters *et al.*, 2012; Pouzet, Didriksen, & Arnt, 2002; Nikiforuk *et al*, 2013). This research has led to the development of medicines such as Lurasidone, a safe and effective treatment approved for sale in the US in 2010 (Nakamura *et al.,* 2009; Meyer, Loebel, & Schweizer, 2009)

**5-HT7 and Sleep.** The 5-HT7 receptor has been implicated in mediation of wakefulness and the sleep cycles. 5-HT7 knockout mice have been shown to spend less time in REM sleep. Furthermore, antagonists, both orally administered and directly infused to various nuclei within the midbrain, pons, and basal forebrain, have been show to increase wakefulness and decrease REM (Hedlund *et al.*, 2005). These interventions additionally led to accumulation of cyclic AMP in cortical regions, a compound often correlated with models of sleep deprivation (Thomas *et al.*, 2003). However, a few agonists for 5-HT7 have also induced wakefulness and decreased REM, suggesting that the ligand-receptor interaction is more complex than a two-state, on-off model (Monti & Jantos, 2014).

**5-HT7 and Depression & Mood.** Related to sleep and circadian rhythms, increasing evidence has also implicated 5-HT7 in mood disorders including depression. Various studies have shown that functional knockout of 5-HT7 receptors and antagonists to 5-HT7 are capable of inducing antidepressant behaviors in acute and chronic mouse models of depression, as measured by tasks such as the tail suspension and forced swimming test (Wesolowska *et al.*, 2006; Cates *et al*., 2013). Interestingly, one study also demonstrated that the antagonist effect was significant only when tests were conducted in the dark, supporting the idea that 5-HT7 has circadianinfluence (Guscott *et al.*, 2005). In addition to behavioral effects, antagonists to 5-HT7 have also been implicated in regulating neuronal morphology and improving hippocampal neurogenesis, an effect that is also commonly associated with antidepressants (Nandam, Jhaveri, & Bartlett, 2007) A number of antidepressents have since undergone clinical trials, leading to successful treatments such as Vortioxetine (which acts on a number of serotonin receptors) on the market today (Garnock-Jones, 2014).

**5-HT7 and Cardiovascular.** The 5-HT7 receptor seems to have some interaction with the cardiovascular system. It is expressed in cardiac muscles and surrounding vasculature and has been shown to regulate the flow of blood within tissues and organs of the body. Activation of the receptor induces tachycardia as well as hypotension through vasodilation (De Vries *et al.*, 1999, Villalon *et al.*, 1997). Conversely, antagonist of the receptor leads to increased mean arterial pressure and hypertension (Damaso *et al.*, 2007).

**5-HT7 and Pain.** The 5-HT7 receptor is expressed by primary afferent fibers and GABAergic neurons in the spine, suggesting a potential role in the sensory system (Viguier *et al.*, 2013). A review of the literature surrounding this field has demonstrated differential mediation of various sources of pain (cites). In regards to localization, injections of agonists for 5-HT7 have induced antinociceptive effects at the spinal cord but pronociceptive effects in the peripheral nervous system (Brenchat *et al.*, 2012). Accordingly, spinal administration of antagonists was shown to block antinociceptive effects of morphine, signifying that they may interact through similar pathways (Dogrul, Ossipov, & Porreca, 2009). In regards to quality of pain, agonists were able to markedly reduce thermal pain but were ineffective against mechanical pain (Viguier *et al.*, 2012). These results suggest that neuronal phenotypes may play a role in determining the modulatory action of 5-HT7 ligands.

**Discussion**

In the current work, wWe capitalized on text mining and co-occurrence analyses to uncover and summarize important relationships between serotonin receptors and their behavioral functions, based on an extensive corpus of serotonin literature. Utilizing a multi-step rule algorithm, we identified receptors with high precision and coverage, and combined these results with keyword-based searches of specific topics of study in order to identify significant positive co-occurrence relationships. Overall, our results yielded 69 significant co-occurrences, with significant behavioral topic relationships found for all but one of our 14 serotonin receptors of interest. These results then guided our literature review elucidating the specific lines of research which may have contributed to these relationships existing in our corpus of causal 5-HT receptor literature.

Our meta-analytic findings and reviews provide several key takeaways. First, while much research aims to assess serotonin broadly without attention to receptor subtypes, the current meta-analysis validates the need for attention to be given to the study of specific receptors. Second, our results may provide an informative guide for future research on serotonin receptors. We highlight several critical receptor-function relationships which have been explored, and briefly discuss the current state of research on those relationships. These quantifiably distinct relationships may therefore be of assistance to researchers designing novel studies within the research domain of 5-HT. Third, our work builds on contemporary efforts to further blend neuroscience with natural language processing, and on more general efforts to examine and analyze large bodies of scientific literature using natural language computational approaches. By performing a straightforward assessment of the significance of co-occurrences between receptors and a set *a priori* list of behavioral topics, our study demonstrates the ability of text mining analyses to examine key patterns and trends in important neuroscientific domains, such as that of serotonin.

**Limitations.**

Importantly, theIt is worth mentioning several notable limitations of the current work. First, we emphasize that the significant receptor-function relationships here do not necessarily capture causal relationships, as our findings are based only off of textual co-occurrence. Put simply, we acknowledge that just because a receptor and a topic occur together in a text does *not* mean that these two are necessarily causally linked. Indeed, our approach does not take into account the specific findings of each study, nor the context in which the receptor or behavior term is used (other than that both appear in the abstract). However, since our corpus consists of nearly 10,000 studies, we believe that our findings still broadly capture substantial trends in the rich literature. Our meta-analytic results alone should not be interpreted as necessarily insinuating any causal relationships. Our literature reviews on each of our notable relationships are therefore designed to further speak to the functional significance of our statistically significant findings. Nonetheless, it is important to note that these relationships may be in part due to various factors unrelated to any underlying causal relationship between receptor and function, such as the kinds of studies which are better funded.

Second, we do not take into account the negation of functions – for example, if a receptor and a behavior are often co-occurring in literature because of a *lack* of causal relationship. Based on our literature reviews, we suspect that such a textual relationship is unlikely – however, such co-occurring mentions may still have impacted our meta-analytic results.

Third, our keyword procedure is inherently limited by our *a priori* selection of behavioral topics of interest (see Appendix 2). Since we had strong priors about particularly relevant and interesting relationships to identify, we decided to utilize discrete keywords in our text mining procedure, rather than rely on attempting to find latent relationships via procedures such as topic modeling. Instead, this approach is limited by the specific use of key word strings and phrases. Furthermore, our procedure was limited to assessing co-occurrence relationships in text abstracts – while full-text text mining is often preferred (see Westergaard et al., 2018), we believe that our use of only abstracts helped narrow-down our analyses to examine only the receptors and topics truly essential to each study in our corpus. Regardless, a full-text assessment of the literature may still yield more thorough results.

Fourth, co-occurrence-based methods of text analysis have been critiqued as simplistic and potentially error-prone (Cohen & Hunter, 2008). However, incorporating rule-based systems within a co-occurrence analysis reduces such risks. In particular, co-occurrence of serotonin receptors and functions in a text must be able to handle variability in how receptors or topics are expressed – for example, 5-HT1A may be written as 5HT1A, 5HT(1A), 5-HT1A, or a multitude of other variants. The topic *depression* may be referenced with words such as *depressed*, *depressive*, and so on (see Cohen & Hunter, 2008; French et al., 2009). Thus, our rule-based regular-expression system enables these variant cases to also be captured in our co-occurrence analyses.

**Future directions.**

The current work also gives way to several interesting lines of future research. As previously alluded to, future studies may attempt to identify latent relationships between words using topic modeling procedures (e.g., Wang & Blei, 2011). While such an approach would make it difficult to assess any *a priori* topics, it would perhaps illuminate any key patterns in the literature unexamined by more surface-level text mining procedures such as co-occurrence analyses.

Although our meta-analytic findings specifically examined relationships between receptors and behavioral topics, there are other important variables that may be assessed via similar analyses. For instance, our original procedure also documented instances of variables such as causal methods, key agonists and antagonists, and the animal model of study (see Supplements). Thus, future research may also assess any key relationships or usage trends with regards to these variables and specific receptors. Also unexamined in the current work are significant negative co-occurrence relationships (i.e., where co-occurrence was significantly lower than expected at chance). Such relationships could also be important to analyze, and may give way to promising future directions.

Finally, it is our hope that researchers adapt the general procedures utilized in this current study to explore textual data and relationships in any number of neuroscientific fields. Our analyses look specifically within the domain of serotonin. However, future textual meta-analyses may examine any number of neuroscientific topics, patterns, and trends, taking advantage of the extensive bodies of literature existing on online databases.

**Conclusion.**

Ultimately, our work explored, analyzed, and summarized key relationships between serotonin receptors and behavioral topics of interest based on the large body of literature on causal interventions on serotonin receptors. We find that serotonin receptors have notably distinct associations with various behaviors, and our findings and literature reviews speak to the complexity of these relationships. Overall, the current research may help inform future studies within both the domain of serotonin, as well as the use of combining text mining and scientific literature more broadly.

**References**

[see margins – to add at very end XX]

**Appendix 1**

*Full Search Criteria:*

(((5-HT1A) OR (5-HT1B) OR( 5-HT1D) OR (5-HT1E) OR (5-HT1F) OR (5-HT2A) OR (5-HT2B) OR (5-HT2C) OR (5-HT3) OR (5-HT4) OR (5-HT5A) OR (5-HT5B) OR (5-HT6) OR (5-HT7) OR (5HT1A) OR (5HT1B) OR (5HT1D) OR (5HT1E) OR (5HT1F) OR (5HT2A) OR (5HT2B) OR (5HT2C) OR (5HT3) OR (5HT4) OR (5HT5A) OR (5HT5B) OR (5HT6) OR( 5HT7)) AND (agonist OR antagonist OR agonism OR antagonism OR optogenetics OR positron emission tomography OR PET OR staining OR stimulation OR knockdown OR knockout OR immunohistochemistry) AND (brain))

**Appendix 2**

*Full Topics Search List:*

Mood; Appetite; Sleep; Locomot; Gastrointestin; Cognit; Memory; Learning; Depress; Anxiety; Anxiolyt; Anxiogen; Psychedel; Psychosis; Schizophreni; Feed; Groom; Psychostim; Impulsiv; Aggressi; Pain; Suicide; Social dominance; Analgesi; Vasoconstrict; Cardiovascular; Empathy; Emesis; Sex; Parkinson’s; Obesity; Nausea; Alzheimer’s; Dementia; Stress; Compulsiv; Addict